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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,893	02/27/2006	Jean Pierre Plouet	0508-1134	2413

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
12/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/530,893	PLOUET ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/21/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 9/21/09, is acknowledged.

2. Claims 36 are pending and under examination in the instant application.

3. Applicant's IDS, filed 9/21/09. is acknowledged.

4. In view of the amendment filed on 9/21/09, only the following rejection is remained.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claim 36 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Saito et al. Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 257) in view of Concina et al (J Vasc Res. 2000 May-Jun;37(3):202-8) for the same reasons set forth in the previous Office Action mailed 5/21/09.

Applicant's arguments, filed 9/21/09, have been fully considered, but have not been found convincing.

Applicant submits that the combination of the teachings of SAITO et al. in view of CONCINA et al. should be considered to teach away, since the combination of the teachings of these two documents would lead the skilled artisan in direction divergent from the path that was taken by the applicant (see In re Gurley, 27 F.3d 551, 31 U.S.P.Q.2d 1130 (Fed. Cir.1994)).

The Office Action argues that HUVEC and FBAEC treated with angiogenic factors have to be considered both as endothelial cells with angiogenic phenotype. At the filing date of the present application, the skilled person would know that many endothelial cells derived from veins, arteries, or arterioles can be used to provide, after stimulation with angiogenic phenotype, endothelial cells with an angiogenic phenotype.

Therefore, the posited document combination can be extended to other endothelial cells derived from veins, arteries, arterioles, placenta, capillary, retina, etc.
At the time the invention was made, the skilled person knew that endothelial cells used as model for studying in vitro angiogenesis are, for instance, the following ones: (see for example Table 1 of VAILHE et al., Laboratory Investigation, 2001, Vol. 81, No. 4, pp: 439-452, attached),

Table 1 of VAILHE et al. teaches that all the above mentioned cells can be used for in vitro angiogenesis and vasculogenesis. More precisely, Table 1 of VAILHE et al. teaches that BAEC (from fetal or calf) are spontaneously able to induce morphogenesis when they are seeded on plate without cellular matrix component.
On the contrary, HUVEC cells and BREC cells are spontaneously able to induce morphogenesis when they are seeded on plate coated with fibrin. Applicant concluded that VAILHE et al. teach that BREC cells and HUVEC cells are the closest ones, in terms of angiogenic potentialities, compared to FBAEC. Consequently, the skilled person would be motivated from the teaching of VAILHE et al., to replace HUVEC cells taught in the method by SAITO et al., by BREC cells instead of FBAEC cells.

Contrary to Applicant's arguments, a prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). Here in contrast to applicant's assertions of teaching away by the prior art because both Concina et al and Vailhe et al references indicate that FBAEC cells as an in vitro model of angiogenesis and vasculogenesis (see table 1, row 4 of Vailhe and Fig. 3 of Concina et al), Concina et al show FBAEC cells to be sensitive to E2 stimulation in a dose-dependent manner; there is no discouragement nor skepticism in the prior art for the use of FBAEC cells in terms of angiogenic potentialities, particularly in light of the prior art teachings to provide the number of cells as a model for angiogenesis and vasculogenesis including FBAEC.

Applicant acknowledges that one of skill in the art would have known that BREC cells stimulation by oestradiol induces VEGF gene expression, in a dose dependant manner, and also induces VEGF protein expression, as indicated respectively in Figure 4 and Figure 5 of SUZUMA et al., reproduced below (Investigative Ophtalmology & Visual Science, 1999, Vol 40, n. 9, pp: 2122-2129, Figs. 4&5).

Thus, VAILHE et al. teach that BREC cells and HUVEC cells are the closest ones, in terms of angiogenic potentialities, compared to FBAEC. Consequently, the skilled person would be motivated from the teaching of VAILHE et al., to replace HUVEC cells taught in the method by SAITO et al., by BREC cells instead of FBAEC cells. Applicant concluded that from the teachings of SUZUMA et al. and the teachings of VAILHE et al., the skilled person would be motivated to use BREC cells of SUZUMA instead of FBAEC cells of CONCINA et al. to produce antibodies directed against tumor vasculature as disclosed in SAITO et al.

While Vailhe et al teaches that BAEC (fetal and calf) can be used in *in vitro* models of angiogenesis and vasculogenesis (see table 1, row 4), Suzuma et al uses the calf BAEC to study the effect of oestradiol on the induction of VEGF gen pxpression. Concina et al use the fetal BAEC to also study the effect of E2 on VEGF content in conditioned medium of FBAEC. According to Vailhe both fetal and calf BAEC can be used for in vitro models of angiogenesis and vasculogenesis, thus fetal and calf BAEC are interchangeable as an in vitro model for angiogenesis and vasculogenesis.

Applicant submits that when substituting SAITO et al. cells by either SUZUMA et al. cells or CONCINA et al. cells, the skilled person would be led in direction divergent from the path that was taken by the applicant. Indeed, pending claim 36 sets forth that "**said endothelial cells having an angiogenic phenotype being obtained by culturing endothelial cells removed from an aorta in a medium consisting essentially of oestradiol and VEGF, said endothelial cells with an angiogenic phenotype being such that.., their expression of VEGFR-2 is increased 4-fold in comparison with cells with a non-angiogenic phenotype**" (emphasis added by Applicant). SUZUMA et

al. teach that oestradiol treated BREC cells are able to express VEGF growth factor, but also VEGFR-2 receptor. Moreover, at an oestradiol dosage of 10^{-8} M (i.e., 10 nM), the level of VEGFR-2 mRNA is increased 2.4 ± 0.3 times compared to untreated BREC cells. This increase corresponds to the maximal increased at this dosage (see page 2126, second column, first paragraph). In contrast to the teachings of SUZUMA et al., CONCINA et al. never mention that the oestradiol stimulation enhances VEGFR-2 gene expression, or the level of said enhancement, if it exists. Without such information, one of skill in the art would be led to prefer SUZUMA et al. cells instead of CONCINA et al. cells.
Consequently, at the time the invention was made, one of ordinary skill, having a knowledge of all the prior art, would be seek to provide a method for producing antibodies specifically interacting with endothelial cells having angionenic phenotype, by using SUZUMA et al. BREC cells stimulated with oestradiol, and secreting VEGF. However, since one of the main features of the endothelial cells having an angiogenic phenotype used in this method is missing, the skilled person would be led in a direction divergent from the path that was taken by the applicant.

However, the expression of VEGFR-2 is increased 4-fold is material claim limitation, the statement of the intended result of supplementing oestradiol and VEGF does change VEGFR-2 expression or otherwise limit the claim. However, a person having ordinary skill in the art would have found it obvious to determine the optimum values of result-effective variables known in the art. The claimed angiogenic phenotype "expression of VEGFR-2 is increased 4-fold in comparison" of the FBAEC does not result in a manipulative difference in the method steps of the claims. The recitation of "expression of VEGFR-2 is increased 4-fold in comparison with cells with a non-angiogenic phenotype" is a statement of the intended results of the treatment of the FBAEC with oestradiol and VEGF, the combined reference teaching arrived to the use of oestradiol treatment which induces the release of VEGF. Finally, the rejection was not made over Suzuma or Vailhe but rather was made over Concina et al. Applicant's arguments with respect to Suzuma and Vailhe are irrelevant to the rejection of record.

Applicant submits that since the cells used for the implementation of the method of SAITO et al. are different, the resulting monoclonal antibodies obtained by the method of SAITO et al. will be consequently different.

However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Attention should also be drawn to the fact that BREC cells are used in the application as filed, as negative control. It is discussed in the Examples Section of the specification that FN cells have an increase of the VEGFR-2 mRNA expression compared to F/O cells, whereas the expression of VEGFR-2 mRNA is identical in BREC/0 and BREC/V (Hutchings et al., 2002). The explanation is that Hutchings et al.'s BREC cells BREC/V have been stimulated, and thus activated, by the VEGF growth factor **ONLY**.

It is not clear why Applicant's arguments are relevant to the rejection of record. Concina et al teach that thoratic aorta VEGF content was increased in E-2-treated rats compared to control rats (see abstract). Concina et al teach VEGF quantification in the conditioned media of FBAE revealed that E2 was able to induce VEGF synthesis in a dose-dependent fashion (see page 204,

2nd col., last sentence, and Fig. 3). Fig. 3 shows the effect of E2 on VEGF content in conditioned medium of FBAEC, wherein FBAEC were incubated with E2 for 48hrs.

Applicant submits that the inventiveness of the present invention resides, in part, in the fact that for the first time endothelial cells with angiogenic phenotypes that have been stimulated by **only two exogenous** growth factor and hormones: VEGF and oestradiol. This particular growth factor and hormone stimulation confer to the cells specific new and inventive characteristics, allowing to obtain a new and inventive method for producing antibodies specifically directed against tumor vasculature.

However, Concina et al teaches the effect of exogenous oestradiol on the endogenous VEGF synthesis and the endothelial cell angiogenic phenotypes. The skilled in the art would be motive to use both VEGF and oestradiol exogenously.

Finally, if the skilled person has been motivated, for any reason, to combine the teachings of SAITO et al. and the teachings of CONCINA et al., the skilled artisan would obtain a method for producing monoclonal antibodies directed against endothelial cells having angiogenic phenotype, but the endothelial cells having angiogenic phenotype obtained would never have **an expression of VEGFR-2 increased 4-fold in comparison with cells with a non-angiogenic phenotype**. Indeed, one of the aims of the present invention is the importance of the exogenous addition of VEGF in the cell culture medium, which has a significantly higher efficacy than the VEGF secreted in response to oestradiol treatment. Consequently, a person with ordinary skilled would never obtain the present invention, as claimed, from a knowledge of the teachings of SAITO et al. and the teaching of CONCINA et al. A prima facie case of unpatentability has thus not been made.

However, it would be conventional and within the skill of the art to identify the exact expression profile of the VEGFR-2. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. The determination of the optimal expression profile of the VEGFR-2 in the VEGF and E2 treated FBAEC is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention.

Applicant's request for interview, filed 9/21/2009, is acknowledged. This Office Action is sent in a timely manner due to the administrative procedures. Applicant is encouraged to contact the Examiner to arrange an interview if still deemed appropriate after receiving this Office Action.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 21, 2009

/Maher M. Haddad/
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